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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/410,462	10/01/99	WILLIAMS	A

EXAMINER	
SORRELL O.F	
ART UNIT	PAPER NUMBER
1633	11

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Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Applicati n No.	Applicant(s)	
	09/410,462	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Eleanor Sorbello	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Response to amendment

1. Applicant's amendment and response to the official Office Action mailed September 15, 2000 as Paper No. 7, has been received and filed on March 29, 2001, as Paper No. 10B. Claims 1-28 are pending. Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow.

2. Examiner apologizes that the sequence compliance letter mailed out to applicants was done erroneously and as applicant's note, a sequence listing is not required and has not been furnished in the instant application.

3. Applicant's arguments are addressed below on a per section basis. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1-24 stand rejected under 35 USC § 112, first paragraph for reasons of record. Applicant's arguments have been fully considered but they are not persuasive.

Applicants' argue (see Response page 3, lines 7-14, dated March 15, 2001) that they are enabled for that which was claimed, and direct examiner to Example 3. However, examiner contends that the claims are not directed to the reduction in size of tumor by direct injection of the adenovirus of the instant invention, for which applicants have been enabled, see (III) of first office action on merits page 3, dated 9/15/00. Examiner maintains that Example 3 does not teach that which is claimed, ie. in a cell population comprising dividing and quiescent cells, a method for substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells. By

direct injection of the adenovirus into the tumor, applicants were not targeting quiescent cells but only dividing cells *in vivo*, and thus did not teach that which is claimed.

Applicants also direct examiner to Example 4, (See Response page 3, paragraph 2, dated March 15, 2001), wherein intranasal inoculations of the mutant or wild type adenovirus of the instant invention were made. Applicants show that the mutant adenoviruses divide less in the quiescent lung cells than the wild type virus. However, examiner notes that this is only a comparison of wild type and mutant adenoviruses in quiescent cells *in vivo* and not that which is claimed, which is a method for substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells *in vivo.*

With regards to the issue that E1A-CR2 Rb binding site mutants selectively and substantially kill proliferating micro-vascular endothelial cells whereas they do so to a much less extent in quiescent micro-vascular endothelial cells, applicants argue that their *in vitro* results can be extrapolated to that which occurs *in vivo*. (see Response page 4, paragraph 2, dated March 15, 2001). Applicants also direct examiner to numerous recent articles that applicants attest that the killing properties of adenoviruses have been taught, and therefore, applicants of the instant invention should be enabled for that which is claimed in the instant application. However, examiner contends that that is not the point in contention. The point that applicants are required to teach via *in vivo* examples is that in a cell population comprising dividing and quiescent cells, a method for substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells.

In the absence of *in vivo* examples in an art accepted model in which applicants teach a method wherein dividing cells and not quiescent cells are infected with E1A-CR2 Rb binding site mutants, and wherein the dividing cells infected with the E1A-CR2 Rb binding site mutants are selectively and substantially killed, and not the quiescent cells, applicants are not enabled for that which they claim. Therefore, the claims stand rejected under 35 U.S.C. 112 first paragraph due to the same reasons of record.

5. Claims 21-28 stand rejected under 35 USC 103(a) for reasons of record. Applicant's arguments have been fully considered but they are not persuasive.

Claims 21-28 are directed to pharmaceutical compositions comprising a Rb binding site adenoviral mutant in a physiological composition; or a pharmaceutical composition comprising adenoviral mutant wherein mutant is dl922/947; or wherein the mutant is pm928; or a composition comprising a Rb binding site adenoviral muant with a negative selection agent operably linked to a promoter.

The above pharmaceutical composition claims, are directed to compositions, because the pharmaceutical language recited in the claims does not impart any particular or new feature, this is interpreted as an "intended use". The composition has no other components other than the components of the vector and a pharmaceutically acceptable carrier. Plasmid vectors are routinely stored in buffers that would be pharmaceutically acceptable. Therefore, this is considered obvious.

Therefore, the claims recite merely adenoviral vectors such as an Rb binding site adenoviral mutant; adenoviral mutant wherein mutant is dl922/947; or wherein the

mutant is pm928; a Rb binding site adenoviral muant with a negative selection agent operably linked to a promoter.

Therefore, as stated in the first office action on merits, Bischoff et. al., Whyte, et al., Jelsma and Moran teach the adenoviral mutants claimed in the instant invention.

Applicants argue that the rejection under 35 U.S.C. 103(a) should be removed as examiner in hindsight has stated that it would have been obvious to one of skill in the art to use these adenoviruses for selectively killing neoplastic or dividing cells in a mixed cell population. However, examiner contends that this is not required of the claims being examined as stated above. The only requirements for the 103(a) rejection required the components of the vector or the adenoviruses claimed.

Therefore, claims 21-28 stand rejected.

6. Applicants request examiner to substitute new drawing sheets Figures 3C-4B, on sheets 5/7, 6/7 and 7/7, for the originally filed drawings. However, examiner does not see the difference between the new drawing sheets and the previously filed drawings. If differences exist, applicants should point it out to examiner.

Conclusion

7. Claims 1-28 stand rejected.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

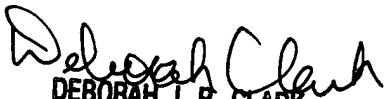
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



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